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 NEWS  5  DEC 14  2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
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 NEWS  7  DEC 21  IPC search and display fields enhanced in CA/CAplus with the
                  IPC reform
 NEWS  8  DEC 23  New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                  USPAT2
 NEWS  9  JAN 13  IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13  New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                  INPADOC
 NEWS 11  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17  IPC 8 in the WPI family of databases including WPIFV
 NEWS 13  JAN 30  Saved answer limit increased
 NEWS 14  JAN 31  Monthly current-awareness alert (SDI) frequency
                  added to TULSA

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
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FILE 'HOME' ENTERED AT 11:58:12 ON 10 FEB 2006

=> file caplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21
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FILE COVERS 1907 - 10 Feb 2006  VOL 144 ISS 8
FILE LAST UPDATED: 9 Feb 2006  (20060209/ED)

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=> s mc 192 or (MC192)
         33493 MC
          2040 MCS
         34960 MC
                 (MC OR MCS)
         30687 192
             3 MC 192
                 (MC(W)192)
            12 MC192
L1           15 MC 192 OR (MC192)

=> s cancer? or neoplas? or tumor
=> s cancer? or neoplas? or tumor?
        283169 CANCER?
        438119 NEOPLAS?
        417183 TUMOR?
L2      690968 CANCER? OR NEOPLAS? OR TUMOR?

=> s l1 and l2
L3           0 L1 AND L2

=> file pctfull
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                12.62      12.83

FILE 'PCTFULL' ENTERED AT 11:59:34 ON 10 FEB 2006
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FILE LAST UPDATED:         3 JAN 2006      <20060103/UP>
MOST RECENT UPDATE WEEK:       200552        <200552/EW>
FILE COVERS 1978 TO DATE

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    DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION
    ABOUT THE IPC REFORM <<<

=> s mc 192 or (MC192)
         32880 MC
          2921 MCS
         35224 MC
                 (MC OR MCS)
         65659 192
             4 MC 192
                 (MC(W)192)
            11 MC192
L4           14 MC 192 OR (MC192)

=> s cancer? or neoplas? or tumor?
         74539 CANCER?
         21534 NEOPLAS?
         62442 TUMOR?
L5       93014 CANCER? OR NEOPLAS? OR TUMOR?

=> s l4 and l5
L6           11 L4 AND L5

=> s conjugat? or coupl? or link? or attach?
         71814 CONJUGAT?
        314207 COUPL?
        285938 LINK?
        353436 ATTACH?
L7      617080 CONJUGAT? OR COUPL? OR LINK? OR ATTACH?

=> s l7 and l6
L8           11 L7 AND L6

=> s l8 not py>2000
        550224 PY>2000
L9            5 L8 NOT PY>2000

=> s l9 not py>1999
        630082 PY>1999
L10           4 L9 NOT PY>1999

=> s anticancer or (anti () cancer) or chemotherap
=> s anticancer or (anti () cancer) or chemotherap?
         13132 ANTICANCER
             9 ANTICANCERS
         13135 ANTICANCER
                 (ANTICANCER OR ANTICANCERS)
        167501 ANTI
           165 ANTIS
        167532 ANTI
                 (ANTI OR ANTIS)
         70375 CANCER
         27076 CANCERS
         72542 CANCER
                 (CANCER OR CANCERS)
         10909 ANTI (W) CANCER
         29221 CHEMOTHERAP?
L11      38810 ANTICANCER OR (ANTI (W) CANCER) OR CHEMOTHERAP?

=> s l10 and l11
L12           1 L10 AND L11

=> d ibib
```

L12 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997021732 PCTFULL ED 20020514
TITLE (ENGLISH): DESIGN OF HORMONE-LIKE ANTIBODIES WITH AGONISTIC AND ANTAGONISTIC FUNCTIONS
TITLE (FRENCH): OBTENTION D'ANTICORPS SIMULANT DES HORMONES ET AYANT DES PROPRIETES D'AGONISTE ET D'ANTAGONISTE
INVENTOR(S): SARAGOVI, H., Uri;
LeSAUTER, Lynne
PATENT ASSIGNEE(S): McGILL UNIVERSITY;
SARAGOVI, H., Uri;
LeSAUTER, Lynne
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9721732	A1	19970619

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1996-CA815 A 19961206
PRIORITY INFO.: GB 1995-9525180.7 19951208

=> d kwic

L12 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN . . . the NGF
docking site. Such antibodies may be used for the treatment, diagnosis or prevention of neurological
diseases, neuromas and neoplastic tumors which
express TrkA receptors. Also these antibodies may be
used to develop and screen for pharmaceutical agents which are
agonistic. . .
ABFR . . . des nerfs (FCN). Cet anticorps peut
servir a diagnostiquer ou a soigner des maladies neurologiques, des nevromes et des tumeurs
neoplasiques qui expriment les recepteurs TrkA. Egalement, ces
anticorps peuvent etre utilises pour
developper et evaluer les agents pharmaceutiques qui sont. . .

DETD . . . NGF docking site. Such antibod-
ies may be used for the diagnosis, treatment or pre-
vention of neurological diseases, neuromas and neo-
plastic tumors which express TrkA receptors. Also
these antibodies may be used to develop and screen for
pharmaceutical agents which are agonistic or antago-
nistic. . .
. . .
vivo inhibition of nerve
growth factor binding to TrkA receptor or the inter-
nalization or downmodulation of the receptor, such as
for inhibiting tumor growth in situ, for the treatment
or prevention of neurological diseases, neuromas and
neoplastic tumors which express TrkA receptors, for
mapping hormone-receptor interactive sites and recep-
tor domain-function correlation such as mapping TrkA
docking sites, for screening pharmacological. . .

In accordance with the present invention there is also provided a method for the treatment of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors in a patient, which comprises administering an effective amount of an antibody of the present invention or a functional. . .

. . .

In accordance with the present invention there is also provided a pharmaceutical composition for the treatment of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors, which comprises an effective amount of an antibody of the present invention or a functional fragment thereof in association. . . .

In accordance with the present invention there is also provided a method for the prognosis or diagnosis of human tumors which comprises.

a) biopsy and immunocytochemistry of tumors using the antibody of the present invention and fragments thereof;
or
b) radiolabeling of the antibody of the present invention and fragments thereof and nuclear imaging. . .

In accordance with the present invention there is also provided a method for the treatment of human tumor of a patient which comprises the steps of.

a) coupling cytotoxic agents to the antibody of the present invention and fragments thereof;
b) administering the coupled antibody of step a) to the patient.

. . .

of the central and/or peripheral nervous system, which comprises an effective amount of an antibody of the present invention or a functional fragment thereof coupled to a pharmaceutical agent in association with a pharmaceutically acceptable carrier. The pharmaceutical agent may be selected from the group consisting of radioligands,. . .

. . .

and
Scatchard plot analysis;
Fig. 6 illustrates the protection from apoptotic death by 5C3 and 5C3 Fabs;
Fig. 7 illustrates nuclear imaging of tumors in vivo with 5C3;
Fig. 8 illustrates the survival of TrkA-expressing cells in serum-free media by 5C3 and derivatives;
Fig. 9 illustrates the differentiation/neuritogenesis of human TrkA-expressing cells in serum media;
Fig. 10 illustrates Mab5C3 prevents TrkA-expressing tumor growth in vivo; and
Fig. 11 illustrates the topography of the CDRs of the present invention.

. . .

(Sigma, Saint Louis, MO), anti-phosphotyrosine mAb 4G10 (UBI, Lake Placid,

NY), and anti-PI-3 kinase polyclonal serum (UBI) were purchased, mouse anti-rat p75 mAb MC192 ascites were a gift from P. Barker, and anti-p65 mAb 87 6 was grown in the laboratory.

. . .

products were characterized by SDS-PAGE under non-reducing or reducing conditions (100 mM 2-mercaptoethanol) to >98% purity. Control Fabs from anti-rat p75 mAb MC192 were similarly prepared.

. . .

NaCl, 0.5%
TweenTm-20, pH 7.6) containing 1% BSA (Sigma), and immunoblotted with the indicated primary mAbs- Secondary antibodies were either horseradish peroxidase (HRP) conjugated goat anti-rabbit IgG (HRP-GaR), or goat anti-mouse IgG (HRP-G(xM) (Sigma). For detection the enhanced chemiluminescence (ECL) reagents (Amersham, Oakville, Ont.) were used following. . .

. . .

mAbs, mAb
5C3 Fab fragments, control mAb 192 Fab fragments or serum (final 5% FBS, normal growth conditions). where indicated, Fabs were externally cross-linked with goat anti-mouse Fab (GamFab, Sigma). Wells containing all culture conditions but no cells were used as blanks.

Monomeric 5C3 Fab protection was dose-dependent. However, equivalent or better protective effects were achieved when Fabs were externally
- 24 -
cross-linked with G(xmFab antibodies. Specificity controls included those described in the previous section for whole mAb 5C3, plus 192 Fabs which had. . .

Aberrant expression of trkA mRNA and NGF responsiveness have been correlated with neurodegenerative disorders and neoplastic malignancy. Hence, TrkA-binding agents will be useful clinical tools in diagnosis, prognosis and perhaps treatment of these diseases. Indeed, mAb 5C3 binding is a positive prognostic marker for certain human neoplasias.

. . .

in neuroblastoma
Neuroblastomas* Number Positive Mixed Negative
Group 1 60 38 17 5
Group 2 53 1 3 5 35
*15 samples repeated after chemotherapy, at the time of second surgery or recurrence: 5C3 staining patterns remained unchanged in 14 tumors; 1 negative tumor sub-
sequently positive post chemotherapy in regions of maturing elements.

- 25 -
Table 7
TrkA expression in other malignant tumors
Malignant tumor N=42 TrkA-Pos
Central nervous system tumors 6 0
Rhabdomyosarcomas 5 0
Primitive neuroectodermal tumors 6 0
Ewing's sarcomas 2 0
Wilm's tumors 6 1
Osteosarcomas 4 0
Melanomas 5 0

Breast carcinomas 5 0
Lung carcinomas 3 0
Table 8
TrkA detection by immunocytochemistry, RT-PCR
and western blot
IMMUNOCYTO. N. . .

Thus, artificial ligands of TrkA can induce receptor internalization and could be useful in delivering toxic agents to the cytoplasma of TrkA-expressing tumors.

TrkA-expressing neuronal 4 6 cells or fibroblastoid E25 cells undergo apoptotic death in serum f ree media but can be rescued. . . combined at suboptimal doses, as would be expected if mAb 5C3 bound and activated unoccupied TrkA receptors. Furthermore, morphological changes and increased attachment to plastic were observed in both the NGF and 5C3 treated cells.

Monomeric 5C3 Fabs protected E25 and 4 6 cells from apoptotic death. When Fabs were externally cross-linked using anti-Fab antibodies, a heightened response occurred. Since growth factor receptor activation requires bivalent binding, the monomeric 5C3 Fabs must have retained. . .

EXAMPLE I
PRELIMINARY STUDY OF THE EFFECT OF mAb 5C3
IN TUMOR GROWTH
Nude mice were injected subcutaneously (right abdominal side) with 2X106 human TrkA expressing tumor cells. Two days post-injections tumors in all mice had begun to form. Mice were randomized prior to treatment. A total of four intraperitoneal injections of 100 micrograms. . .

The mAb 5C3 dramatically reduced the primary tumor weight with no observable metastatic invasion. A small fibrotic mass was localized at the site of injection in mAb 5C3 treated mice. In contrast, IgG treated mice had large, vascularized tumor masses, which metastasized to the liver, peritoneum gut and spleen. All animals had similar body weights ('30 grams).

Table 9
TREATMENT PRIMARY TUMOR WEIGHT METASTASIS WEIGHT
(mg) mg)
5C3 mAb 50 ± 20 (fibrotic) NONE
mouse IgG 800 ± 250 350 ± 20
EXAMPLE II
The use of Mab SC3 and its derivatives for the diagnosis, prognosis and localization of tumors
The in vivo targeting ef f icacy of agents that bind the NGF receptor p140 TrkA was evaluated.

Nuclear imaging studies were done after the injection of 99mTc-labeled compounds in nude mice bearing tumors. Kinetics of tumor targeting, blood clearance,
and bioavailability were studied. Tumors that do not express TrkA were not targeted, demonstrating the

specificity in vivo. This biodistribution study demonstrates that receptor-specific molecule analogs may be useful and may be effective agents for the detection, diagnosis, and possible treatment of neoplasias involving overexpressed oncogenic receptors such as TrkA (Fig. 7).

99mTc-[SC3]
Ligand % id/g T/nT
tumor 1.25 1
blood 0.1 13
muscle 0.06 20
heart 0.10 13
lung 0.17 7.30
liver 0.61 2.10
spleen 0.13 9.42
kidney 1.48 0.9
large bowel 2.2 0.7

EXAMPLE III

5C3. . . relevant for binding TrkA. These were named CDR1, CDR2, and CDR3. Region CDR1 is connected to CDR2 by a 15 amino acid linker; CDR2 is connected to CDR3 by a 30 amino acid linker. Their secondary structures have been analyzed.

Monovalent Fabs of 5C3 obtained after papain digestion are also agonistic, especially when externally cross-linked by anti-Fabs. A smaller fragment of mAb 5C3 called CDR(R) also protects cells from apoptosis (Fig. 8).

. . .
than the 25 kDa NGF molecule and is still agonistic. CDR(R) is composed of 3 selected CDRs (out of 6 possible ones) linked by long spacer regions. Preliminary studies have suggested that actually only 2 of the 3 CDRs are relevant for binding to TrkA. Further, it is expected that even smaller fragments can be designed, e.g. upon removal of the linker regions.

CLMEN 5 The use of claim 3 or 4, for inhibiting tumor growth in situ.

6- The use of claim 3 or 4, for the treatment or prevention of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors.

14 A method for the treatment of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors in a patient, which comprises administering an effective amount of an antibody of claim 1 or a functional. . .

15 A pharmaceutical Composition for the treatment of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors, which comprises an effective amount of an antibody of claim 1 or a functional fragment thereof in. . .

17 A method for the prognosis or diagnosis of human tumor which comprises:

a) biopsy and immunocytochemistry of tumors using the antibody of claim 12 and fragments thereof; or

b) radiolabeling of the antibody of claim 12 and fragments thereof and nuclear imaging. . .

18 A method f or the treatment of human tumor of a patient which comprises the steps of:
a) coupling cytotoxic agents to the antibody of claim 12 and fragments thereof;
b) administering the coupled antibody of step a) to said patient.
. . .
the central
and/or peripheral nervous system, which comprises an effective amount of an antibody of claim 1 or a functional fragment thereof coupled to a pharmaceutical
- 43 -
agent in association with a pharmaceutically acceptable carrier-

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=> f his
        101650 HIS
            22 HISES
L13     101666 HIS
                (HIS OR HISES)

=> file his
'HIS' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'PCTFULL'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
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=> d his

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     FILE 'CAPLUS' ENTERED AT 11:58:33 ON 10 FEB 2006
L1           15 S MC 192 OR (MC192)
L2       690968 S CANCER? OR NEOPLAS? OR TUMOR?
L3            0 S L1 AND L2

     FILE 'PCTFULL' ENTERED AT 11:59:34 ON 10 FEB 2006
L4           14 S MC 192 OR (MC192)
L5        93014 S CANCER? OR NEOPLAS? OR TUMOR?
L6           11 S L4 AND L5
L7       617080 S CONJUGAT? OR COUPL? OR LINK? OR ATTACH?
L8           11 S L7 AND L6
L9            5 S L8 NOT PY>2000
L10           4 S L9 NOT PY>1999
L11       38810 S ANTICANCER OR (ANTI () CANCER) OR CHEMOTHERAP?
L12           1 S L10 AND L11
L13      101666 F HIS

=> s l12
L14          1 L10 AND L11

=> d ibib abs

L14    ANSWER 1 OF 1      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1997021732 PCTFULL  ED 20020514
TITLE (ENGLISH):         DESIGN OF HORMONE-LIKE ANTIBODIES WITH AGONISTIC AND
                         ANTAGONISTIC FUNCTIONS
TITLE (FRENCH):          OBTENTION D'ANTICORPS SIMULANT DES HORMONES ET AYANT
```

DES PROPRIETES D'AGONISTE ET D'ANTAGONISTE

INVENTOR(S): SARAGOVI, H., Uri;
LeSAUTER, Lynne

PATENT ASSIGNEE(S): McGILL UNIVERSITY;
SARAGOVI, H., Uri;
LeSAUTER, Lynne

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9721732	A1	19970619

DESIGNATED STATES

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-CA815 A 19961206

PRIORITY INFO.: GB 1995-9525180.7 19951208

ABEN The present invention relates to an agonistic anti-human TrkA mAb 5C3 which recognizes the NGF docking site. Such antibodies may be used for the treatment, diagnosis or prevention of neurological diseases, neuromas and neoplastic tumors which express TrkA receptors. Also these antibodies may be used to develop and screen for pharmaceutical agents which are agonistic or antagonistic to NGF binding to the TrkA receptors.

ABFR L'invention concerne un anticorps monoclonal (ACm) 5C3 dirige contre le recepteur TrkA humain et reconnaissant le site d'ancrage du facteur de croissance des nerfs (FCN). Cet anticorps peut servir a diagnostiquer ou a soigner des maladies neurologiques, des nevromes et des tumeurs neoplasiques qui expriment les recepteurs TrkA. Egalement, ces anticorps peuvent etre utilises pour developper et evaluer les agents pharmaceutiques qui sont des agonistes ou des antagonistes de la fixation du FCN au recepteur TrkA.

=> d l10 ibib 1-4

L10 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1997021732 PCTFULL ED 20020514

TITLE (ENGLISH): DESIGN OF HORMONE-LIKE ANTIBODIES WITH AGONISTIC AND ANTAGONISTIC FUNCTIONS

TITLE (FRENCH): OBTENTION D'ANTICORPS SIMULANT DES HORMONES ET AYANT DES PROPRIETES D'AGONISTE ET D'ANTAGONISTE

INVENTOR(S): SARAGOVI, H., Uri;
LeSAUTER, Lynne

PATENT ASSIGNEE(S): McGILL UNIVERSITY;
SARAGOVI, H., Uri;
LeSAUTER, Lynne

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9721732	A1	19970619

DESIGNATED STATES

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-CA815 A 19961206
PRIORITY INFO.: GB 1995-9525180.7 19951208

L10 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1994020125 PCTFULL ED 20020513
TITLE (ENGLISH): TREATMENT OF MOTOR NEURON DISEASES WITH FIBROBLAST GROWTH FACTOR-5 (FGF-5)
TITLE (FRENCH): TRAITEMENT DES AFFECTIONS DES NEURONES MOTEURS A L'AIDE DU FACTEUR DE CROISSANCE DES FIBROBLASTES 5 (FGF-5)
INVENTOR(S): HUGHES, Richard, A.;
SENDTNER, Michael;
LINDHOLM, Dan;
THOENEN, Hans, F., E.
PATENT ASSIGNEE(S): MAX-PLANCK-GESELLSCHAFT ZUR FoeRDERUNG DER WISSENSCHAFTEN E.V.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9420125	A1	19940915

DESIGNATED STATES
W: AU CA CN CZ FI HU JP KR NO NZ PL RU SI SK UA AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1994-EP764 A 19940311
PRIORITY INFO.: US 1993-8/030,611 19930312

L10 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992009305 PCTFULL ED 20020513
TITLE (ENGLISH): ANTI CD-4 ANTIBODIES BLOCKING HIV-INDUCED SYNCYTIA
TITLE (FRENCH): ANTICORPS ANTI-CD4 BLOQUANT LES SYNCYTIA PROVOQUES PAR LE VIH
INVENTOR(S): BURKLY, Linda, C.;
CHISHOLM, Patricia, L.;
THOMAS, David, W.;
ROSA, Margaret, D.;
ROSA, Joseph, J.
PATENT ASSIGNEE(S): BIOGEN, INC.;
BURKLY, Linda, C.;
CHISHOLM, Patricia, L.;
THOMAS, David, W.;
ROSA, Margaret, D.;
ROSA, Joseph, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9209305	A1	19920611

DESIGNATED STATES
W: AT AU BE BF BJ CA CF CG CH CI CM DE DK ES FR GA GB GN GR IT JP LU ML MR NL SE SN TD TG US
APPLICATION INFO.: WO 1991-US8843 A 19911127
PRIORITY INFO.: US 1990-618,542 19901127

L10 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1989001975 PCTFULL ED 20020513

TITLE (ENGLISH): RECOMBINANT ANTIBODIES AND METHODS FOR THEIR PRODUCTION
TITLE (FRENCH): ANTICORPS RECOMBINANTS ET LEURS PROCEDES DE PRODUCTION
INVENTOR(S): CATTANEO, Antonino;
NEUBERGER, Michael, Samuel
PATENT ASSIGNEE(S): CELLTECH LIMITED;
CATTANEO, Antonino;
NEUBERGER, Michael, Samuel
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 8901975	A1	19890309

DESIGNATED STATES
W: AT BE CH DE FR GB IT JP LU NL SE US
APPLICATION INFO.: WO 1988-GB695 A 19880824
PRIORITY INFO.: GB 1987-8719963 19870824

=> d l10 ibib kwic 4

L10 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1989001975 PCTFULL ED 20020513
TITLE (ENGLISH): RECOMBINANT ANTIBODIES AND METHODS FOR THEIR PRODUCTION
TITLE (FRENCH): ANTICORPS RECOMBINANTS ET LEURS PROCEDES DE PRODUCTION
INVENTOR(S): CATTANEO, Antonino;
NEUBERGER, Michael, Samuel
PATENT ASSIGNEE(S): CELLTECH LIMITED;
CATTANEO, Antonino;
NEUBERGER, Michael, Samuel
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 8901975	A1	19890309

DESIGNATED STATES
W: AT BE CH DE FR GB IT JP LU NL SE US
APPLICATION INFO.: WO 1988-GB695 A 19880824
PRIORITY INFO.: GB 1987-8719963 19870824

DETD . . . as single
units comprising two heavy and two light chains bound
together in conventional fashion by disulphide.bonds.--
Since IgG is monomeric, it readily attaches to its
antigen, However, it is generally unable to activate
any of the body's effector functions until it is
aggregated.
. . .
derived from one species and a
constant region derived from another species, altered
antibodies, i.e. antibodies having a variable region
from an Ig attached by peptide linkage to a
co-expressed
effector protein, and humanised antibodies, i.e.
. . .
use a gliama cell line as a host cell for
the production of recombinant polymeric IgM. The glioma
cell line is a cancerous cell line derived from glial
cells from within the brain. Glial cells are classified
as actively secreting cells. It is also possible. . .
. . .
or
pancreatic cells, and neural cells, such as pheochromal

cells and, in particular, glial cells. Such actively secreting cells have the advantage that nozmial (non-cancerous) cells can readily be cultured in vitro.

. . .

thus provide a host system for the prcduction of recombinant polymeric IqM which will avoid any problems inherent in the use of cancerous host cells.

. . .

also contains a single intron between the regions encoding most of the leader peptide and the VHDJH region. The transcription unit is linked to a gene encoding guanidine phosphoribosyl transferase (q-pt) which can be used as a selective marker.

. . .

cloned in a derivative of pSV2GPT (1) in which the BamHI site had been converted to a SacI site by use of linkers. The HS-V p 2 transcription unit was assembled in three parts. The promoter/transcription szart region was obtained from plasmid pF1 (2) as. . .

. . .

HOPC 2020 but with the promoter/leader exon replaced by the hs-P70 promoter/VH-leader portion of plasmid pSV-HSVg2. The HSVX1 light chain transcription unit is linked to a gene endowing resistance to neomycin (neo) which can be used as a selective marker.

. . .

derivative of pSV2neo (6) in which the HindIII site has been destroyed by filling in and a new HindIII site created by linker insertion in the BamHI site. The promoter/transcription start/leader region is the same as in pSV-HSV W 2 except in that (i) the region. . .

(i) measuring receptors for nerve growth factor (NGF) (13); fluorescent staining with antibody MC 192 (14); immunoprecipitation of S100 protein (15); and immunofluorescent staining for glial fibrillar acidic protein (16). The PC12 cells were shown to respond to NGF.

Purification on hapten sorbents was carried out using NIP-caproate linked to Sepharose as previously described (9).

. . .

and analysed either after reduction (left panel) on a 7.5% SDS/polyacrylamide gel or unreduced (right panel) on a 4%polyacrylamide gel made using N,N'-diallyltartardiamide to cross-link. The positions of the originr IgMf IgE, IgG, and W markers are indicated.

=> file his
'HIS' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'PCTFULL'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files that are available. If you have requested multiple files, you can specify a corrected file name or you can enter "IGNORE" to continue accessing the remaining file names entered.

=> d his

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     (FILE 'HOME' ENTERED AT 11:58:12 ON 10 FEB 2006)

     FILE 'CAPLUS' ENTERED AT 11:58:33 ON 10 FEB 2006
L1           15 S MC 192 OR (MC192)
L2       690968 S CANCER? OR NEOPLAS? OR TUMOR?
L3            0 S L1 AND L2

     FILE 'PCTFULL' ENTERED AT 11:59:34 ON 10 FEB 2006
L4           14 S MC 192 OR (MC192)
L5        93014 S CANCER? OR NEOPLAS? OR TUMOR?
L6           11 S L4 AND L5
L7       617080 S CONJUGAT? OR COUPL? OR LINK? OR ATTACH?
L8           11 S L7 AND L6
L9            5 S L8 NOT PY>2000
L10           4 S L9 NOT PY>1999
L11       38810 S ANTICANCER OR (ANTI () CANCER) OR CHEMOTHERAP?
L12           1 S L10 AND L11
L13      101666 F HIS
L14           1 S L12

=> s l9 not l10
L15           1 L9 NOT L10

=> d ibib

L15    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2000037103 PCTFULL  ED 20020515
TITLE (ENGLISH):         COMPOUNDS FOR INTRACELLULAR DELIVERY OF THERAPEUTIC
                         MOIETIES TO NERVE CELLS
TITLE (FRENCH):          COMPOSES D'APPORT INTRACELLULAIRE DE GROUPES
                         CARACTERISTIQUES THERAPEUTIQUES A DES CELLULES
                         NERVEUSES
INVENTOR(S):             WEBB, Robert, R.;
                         MCKEE, Constance, A.
PATENT ASSIGNEE(S):      XAVOS;
                         WEBB, Robert, R.;
                         MCKEE, Constance, A.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2000037103         A2 20000629
DESIGNATED STATES
       W:                AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
                         DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE
                         KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX
                         NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
                         UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW
                         AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR
                         GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW
                         ML MR NE SN TD TG
APPLICATION INFO.:       WO 1999-US28211       A  19991129
PRIORITY INFO.:          US 1998-09/217,037       19981221


=> s IR3
L16       1062 IR3

=> s antibod?
L17      84196 ANTIBOD?

=> s l17 and l16
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L18        191 L17 AND L16

=> d his

     (FILE 'HOME' ENTERED AT 11:58:12 ON 10 FEB 2006)

     FILE 'CAPLUS' ENTERED AT 11:58:33 ON 10 FEB 2006
L1           15 S MC 192 OR (MC192)
L2       690968 S CANCER? OR NEOPLAS? OR TUMOR?
L3            0 S L1 AND L2

     FILE 'PCTFULL' ENTERED AT 11:59:34 ON 10 FEB 2006
L4           14 S MC 192 OR (MC192)
L5        93014 S CANCER? OR NEOPLAS? OR TUMOR?
L6           11 S L4 AND L5
L7       617080 S CONJUGAT? OR COUPL? OR LINK? OR ATTACH?
L8           11 S L7 AND L6
L9            5 S L8 NOT PY>2000
L10           4 S L9 NOT PY>1999
L11       38810 S ANTICANCER OR (ANTI () CANCER) OR CHEMOTHERAP?
L12           1 S L10 AND L11
L13      101666 F HIS
L14           1 S L12
L15           1 S L9 NOT L10
L16        1062 S IR3
L17       84196 S ANTIBOD?
L18         191 S L17 AND L16

=> s l18 and l5
L19        154 L18 AND L5

=> s l19 and l7
L20        152 L19 AND L7

=> s l11 and l20
L21         87 L11 AND L20

=> s l21 not py>2000
        550224 PY>2000
L22         28 L21 NOT PY>2000

=> s l22 not py>1999
        630082 PY>1999
L23         20 L22 NOT PY>1999

=> d ibib 1

L23    ANSWER 1 OF 20    PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1999030727 PCTFULL  ED 20020515
TITLE (ENGLISH):        POLYMERIC PRODRUGS OF AMINO- AND HYDROXYL-CONTAINING
                        BIOACTIVE AGENTS
TITLE (FRENCH):         PRODROGUES POLYMERIQUES D'AGENTS BIOACTIFS CONTENANT
                        AMINE OU HYDROXY
INVENTOR(S):            GREENWALD, Richard, B.;
                        PENDRI, Annapurna;
                        CHOE, Yun, H.
PATENT ASSIGNEE(S):     ENZON, INC.
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER             KIND     DATE
                        --------------------------------
                        WO 9930727           A1 19990624
DESIGNATED STATES
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W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT
RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM
AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US26565 A 19981214
PRIORITY INFO.: US 1997-08/992,435 19971217
US 1998-09/183,557 19981030

=> d kwic

L23 ANSWER 1 OF 20 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN . . . to double prodrugs containing polymeric-based transport forms. These polymeric prodrugs are preferably of formula (I) wherein: L1 is a bifunctional linking moiety; in formula (a) B is H, a leaving group, a residue of an amine-containing moiety, or a residue of. . .

DETD . . . AND HYDROXYL-CONTAINING BIOACTIVE AGENTS
TECHNICAL FIELD
The present invention relates to double prodrugs. In particular, the invention relates to polymefic-based double prodrugs having reversible linkages involving amino and hydroxyl moieties of chemical compounds and biologically active materials such as enzymes, proteins and the like.
. . .
as with alkaloids, it has been determined that when only one or two polymers of less than about IO, 000 daltons are conjugated thereto, the resulting conjugates are rapidly eliminated in vivo especially if a somewhat hydrolysis-resistant linkage is used. In fact, such 0 conjugates are so rapidly cleared from the body that even if a hydrolysis-prone ester linkage is used, not enough of the parent molecule is regenerated in vivo. This is often not a concern with moieties such as proteins, enzymes and the like even when hydrolysis-resistant linkages are used. In those cases multiple polymer strands, each having a molecular weight of about 2-5 kDa, are used to further. . .

R14
L, is a bifunctional linking moiety such as Y5
7 R,
or la
f M-C
R8 CFb P
L Jn q
Y,
11
G is H or -C where
B is H, a leaving. . .
. . .
of a biologically active compound which remains after it has undergone a substitution reaction in which the prodrug carrier portion

has been attached.

. . .

capable of solubilizing amine-containing or hydroxyl-containing compounds and extending their half-life as compared to the native or even second prodrug counterparts. The linkage between the polymer 3 0 and the second prodrug compound as described above, hydrolyzes at a rate which 5 allows the compound to. . .

Methods of making and using the compounds and conjugates described herein are also provided.

. . .

R21 r S
9 Y4
RI
RI, Li]]C Y3 L; -y2'-G
f - I
RIO K4
M Ar V
IR t R51 U
wherein: R14
Li is a bifunctional linking moiety such as Y5
R15
7 R7 L Ja
or I
f M-C
R8 4CF42 P
L -J n q
Y,
G is H or where
B is H,. . .

C. LENKER MOIETY LI

As shown above, the invention includes bifunctional linking moiety L, which Y4 11 when combined with C, forms an amino acid residue linker, or when (p) is greater than one, a peptide residue linker.

I I

D. THE DOUBLE PRODRUG LINKAGE PORTION

Y4
The first labile bond of the double prodrug system, which joins the L, to) is selected to hydrolyze, such as via. . .

. . .

methyl or ethyl or substituted C,-6 alkyl. It is preferred that X is either 0 or NR,2-

2. Q Portion of the Linker

Alternatively, when L, includes Q, which is a moiety containing a fi-ee Y4 electron pair positioned three to six atoms from the], moiety, the polymer, RI,, is preferably attached to Q via a heteroatom such as oxygen. In a preferred 12 embodiment, the free electron pair is five atoms from this. . .

In these embodiments, R,, is attached to Q via NR,2, 0, or S. Thus, Q
assists hydrolysis of the prodrug linkage by anchimeric assistance because the free
electron pair moiety can generate a three- to six-membered, but preferably five-
membered, ring by-product upon hydrolysis of the preferably ester linkage.

The linkages included in the compounds have hydrolysis rates in the plasma
of the mammal being treated which is short enough to allow. . .
. . .
the disclosure of each is incorporated herein by reference. It will be understood that the water-soluble polymer will be functionalized for attachment to
the linkage via M, X or Q herein. As an example, the PEG portion of the prodrugs
can be the following non-limiting compounds:. . .

In order to provide the desired hydrolyzable linkage, mono- or di-acid
activated polymers such as PEG acids or PEG diacids can be used as well as mono-
or di-PEG amines. . .
. . .
in the double prodrug must be sufficient so as to provide sufficient circulation of the double prodrug before hydrolysis of the linker.

Within the ranges provided above, polymers having molecular weight ranges of at
least 20,000 are preferred in some aspects for chemotherapeutic and organic
moieties. In the case of some nucleophiles such as certain proteins, enzymes and
the like, polymers having a molecular weight. . .
. . .
form
(IV) with an activating moiety donor such as p-nitrophenyl chloride (PNP-Cl)
(forming, for example, compound (V) in Figure 1); and optionally
e. attaching an amine-containing or hydroxyl-containing compound
residue, e.g. the drug to be transported, to compound (V) by displacing the leaving
group in a. . .
. . .
the first
method above and reacting it with an activating moiety donor such as p-nitrophenyl
chloride (PNP-Cl) forming (VI) in Figure 1;
b. attaching an amine-containing or hydroxyl-containing compound,
e.g. the drug to be transported, to the activated intermediate compound (VI);
1 8
C. removing the protecting. . .

The resulting conjugated prodrug composition is then recovered or isolated using
techniques known to those of ordinary skill, i.e. filtered, recrystallized.

Once in place, the activated form of the PEG prodrug (or blocked prodrug) is ready for conjugation with an amine- or hydroxyl-containing compound.

. . .

Ara-C (cytosine arabinoside) and related anti-metabolite compounds, e.g., gemcitabine, etc. Alternatively, B can be a residue of an amine-containing cardiovascular agent, anti-neoplastic, anti-infective, anti-fungal such as nystatin and amphotericin B, anti-anxiety agent, gastrointestinal agent, central nervous system-activating agent, analgesic, fertility agent, contraceptive agent, anti-inflammatory. . .

Suitable proteins, polypeptides, enzymes, peptides and the like having at least one available amino group for polymer attachment include materials which have physiological or pharmacological activities as well as those which are able to catalyze reactions in organic solvents. The. . .

. . .

factors and phosphólipase-activating protein (PLAP). Other proteins of general biological or therapeutic interest include insulin, plant proteins such as lectins and ficins, tumor necrosis factors and related proteins, growth factors such as transforming growth factors, such as TGFa's or TGFP's and epidermal growth factors, hormones, 23 sornatomedins,. . .

. . .

of a polypeptide demonstrating in vivo bioactivity. This includes amino acid sequences, nucleic acids (DNA, RNA) peptide 2 0 nucleic acids (PNA), antibody fragments, single chain binding proteins, see, for example U.S. Patent No. 4,946,778, disclosure of which is incorporated herein by reference, binding molecules including fusions of antibodies or fragments, polyclonal antibodies, monoclonal antibodies and catalytic antibodies.

. . .

herein is that there is available at least one (primary or secondary) amine 2 0 containing position which can react and link with a carrier portion and that there is not substantial loss of bioactivity after the double prodrug system releases and regenerates the. . .

. . .

incorporation into the double prodrug compositions of the invention, may themselves be substances/compounds which are not active after hydrolytic release from the linked composition, but which will become active after undergoing a further chemical process/reaction. For example, an anticancer drug that is delivered to the bloodstream by the double

prodrug transport system, may remain inactive until entering a cancer or tumor cell,
whereupon it is activated by the cancer or tumor cell chemistry, e.g., by an
25
enzymatic reaction unique to that cell.

After conjugation, the remaining arnine-containing compound is referred to
as the residue of the unconjugated compound.

. . .
trees indigenous to China and nothapodytesfoetida trees indigenous to India. Camptothecin and related compounds and analogs are also
known to be potential anticancer or antitumor agents and have been shown to
exhibit these activities in vitro and in vivo. Camptothecin and related compounds
are also. . .

. . .
The A ring can also be substituted in the 9-position with a straight or branched CI-30 alkyl or C,47 alkoxy, optionally linked to the ring by a heteroatom
i.e.- 0 or S. The B ring can be substituted in the 7-position with a. .
.

. . .
OH moiety which is capable of reacting directly with activated forms of the
polymer transport systems described herein or to the linking moiety intermediates,
e.g. iminodiacetic acid, etc., which are then attached to a polymer such as PEG.

0
2 0 OH
NH
Ph
ACO
5BZ
Paclitaxel: R', C61-15; R'2 CH3CO; Taxotere: R', (CH3)3CO; R'2 H
These derivatives have been found to be effective anti-cancer agents.

. . .
parent compounds include, for example, certain low molecular weight biologically active proteins, enzymes and peptides, including
peptido glycans, as well as other anti-tumor agents, cardiovascular agents such as
forskolin; anti-neoplastics such as combretastatin, vinblastine, doxorubicin, Ara-C,
maytansine, etc.; anti-infectives such as vancomycin, erythromycin, etc.; anti-
fungals such as nystatin, amphoteracin B, triazoles,. . .

. . .
the double
2 0 prodrug compositions of the invention, may themselves be substances/compounds
which are not active after hydrolytic release from the linked composition, but which
will become active after undergoing a further chemical process/reaction. For
example, an anticancer drug that is delivered to the bloodstream by the double
prodrug transport system, may remain inactive until entering a

cancer or tumor cell,
whereupon it is activated by the cancer or tumor
cell chemistry, e.g., by an
enzymatic reaction unique to that cell.

29
After conjugation, the remaining amine-or hydroxyl-containing
compound is
referred to as the residue of the unconjugated compound.
. . .
not only the reversible double prodrug system described
above but also a second polymeric transport system based on more
permanent types
of linkages. The hybrids can be prepared by at least two
methods. For example,
the benzyl-elimination-based double prodrug can be synthesized first and
then
PEGylated using any art-recognized activated polymer such as
thiazolidinyl thione-
or succinimidyl carbonate-activated PEG. Alternatively, the more
permanent
conjugation reaction can be performed first and the resultant
conjugates can be used
to form the double prodrug conjugates described herein. It
will be understood that
the hybrid systems will be better suited for proteins, enzymes and the
like where
multiple amino groups are available for attachment of the
polymeric transport
forms. For purposes of the present invention, activated polymers will be
understood to include polymers containing one or. . .

The activating terminal moiety can be any group which facilitates
conjugation of the polymers with the biologically active
material, i.e. protein,
enzyme, etc. either before of after the double prodrug transport system.
. .
. . .
for, among other things, treating diseases which
are similar to those which are treated with the parent compound, e.g.
enzyme
replacement therapy, neoplastic disease, reducing
tumor burden, preventing
metastasis of neoplasms and preventing recurrences of
tumor/neoplastic growths in
mammals.

Synthesis of (24b): Compound 24b was prepared in a similar manner to
compound 24a using a 40 kDa MW PEG linker 4b in place of MW 5
kDa linker
4a. UV assay for this compound indicated the amount of daunorubicin
present is
2.3 %. In vitro and in vivo results for. . .

Synthesis of compound (26b): Compound 26b was prepared in a similar
manner
to compound 26a using a 40 kDa PEG linker 8b in place of the 5
kDaPEG linker
8a. UV assay for this compound indicated the amount of daunorubicin
present is
2.1 %.

Synthesis of compound (27b): Compound 27b was prepared in a similar
manner

to compound 27a using a 40 kDa PEG linker 6b in place of 5 kDaPEG linker 6a.

. . .

Example 29*

Synthesis of compound (27c): Compound 27c was prepared in a similar manner to compound 27a using a 40 kDa PEG linker 6c in place of 5 kDaPEG linker 6a.

Synthesis of compound (29b): Compound 29b was prepared in a similar manner to compound 29a using a 40 kDa PEG linker 14b in place of the 5 kDaPEG linker 14a. UV assay for this compound indicated the amount of daunorubicin present is 2.1%.

Synthesis of compound (31b): Compound 31b was prepared in a similar manner to compound 31a using a 40 kDa PEG linker 21b in place of the 5 kDa linker 21a.

Con-jugation of compound 2a or 32a to (L)-asparaginase: synthesis of compound (33): PEG linker 2a or 32a (450 mg, 0.084 mmol, 317 eq) was added to native (L)-asparaginase (37.5 mg, 416 gL, 0.00027 mmol) in. . . gentle stirring. The solution was stiffed at 30 'C for 30 minutes. A GPC column (Zorbax GF-450) was used to monitor PEG conjugation: The PEG-Asp conjugate had a retention time of 8.5 min. At the end of the reaction (as evidenced by the absence of native enzyme),. . . . freshly prepared 33 was found to be 137 IU/mg (native asparaginase = 217 IU/mg). Protein modification of asparaginase with SS-PEG (a permanent linker) using a procedure corresponding to that described in the aforementioned U.S. Patent No. 4,179,337 gave a sin-fflar activity of 120 IU/mg. A. . .

Kinetics of hydrolysis of PEG conjugate of (L)-asparaginase (33) in rat plasma and buffer: The rate of hydrolysis of compound 33 in rat plasma was measured using a. . .

Synthesis of (34). a protein hybrid: con-jugation of (33) with SS-PEG (a permanent linker): PEG linker 2a (393 mg, 0.073 mmol, 70 eq) was reacted with native (L)-asparaginase (150 mg, 1.664 m.L, 0.00106 mmol) in 30 m.L. . .

Demonstration of selective removal of reversible PEG linker (2a) from the hybrid (34): Generation of a permanently modified asparaffinasr,, compound (5, 100 mg of 34 is dissoved in 30. . . (Amicon) having a molecular weight cut off of 50,000 Daltons to remove free PEG which was formed by selective cleavage of the conjugates formed from the PEG-2a linker. The solution now contains only

SS-PEG conjugated asparaginase (35). Thus, the revesible
linker is hydrolyzed,
leaving only the relatively perminantly bonded PEG attached to
the asparaginase.

. . .

daunorubicin was given i.p. in balb/c mice bearing
S.C. Madison 109 Lung Carcinoma at I & 4 days after inoculation. The
median
tumor volume of treatment and control groups were measured and
compared when
the control group's median tumor volume reached approximately
2000 mm3.

. . .

was administered intravenously in nude
mice bearing a human ovarian carcinoma xenografts at 1, 5 & 9 days after
inoculation. The median tumor volume of treatment and control
groups were
measured and compared when the control group's median tumor
volume reached
approximately 1000 mm3.
2 0 c William C. Rose. Evaluation of Madison 109 Lung Carcinoma as a
Model
for Screening Antitumor Drugs. Cancer Treatment Reports, 1981,
65, 299.

CLMEN. . . the formula:

I R21 R31 S
Y4
Ri
R11- Ll]] C Y3 C-y2'-G
Rio K4
L Jm Ar _V
wherein: R t R51 U
LI is a bifunctional linking moiety;
YJ
G is H or -C-rs- where
B is H, a leaving group, a residue of an amine-containing moiety, or a
residue of. . .

. . .

claim I 1, wherein A is selected from the group consisting
of hydrogen, C0211, C1-6 alkyl moieties, dialkyl acyl urea alkyls and
IR3]S I R2]r
RI Y4 Rs
G'--Y2-C Y3 C
R4_ Ar Rio
_M
61t
wherein G' is the same as G or another member of the group. . .

. . .

C Y3 C _N 2 B2
I
Ar L M4
IR R51U
wherein M2 is a cleavable or reversible protecting group;
LI is a bifunctional linking moiety; YJ
B2 is selected from the group consisting of H, UH] HU-
and leaving groups;
Y,-4 are independently 0, S, or NR,2
(r),. . .

. . .

step of
e. reacting the prodrug transport form of step d with an amine-
containing or hydroxyl-containing compound residue to form a
conjugate.

. . .
31S
Y
11 I1
M2 i]]C Y3 C_Y2 B2
I
Ar L K4
1R R51U
wherein M2 is a cleavable or reversible protecting group;
LI is a bifunctional linking moiety; YJ
11
B, is selected from the group consisting of H, OH, HC- and leaving groups;
YI-4 are independently 0 or S or. . .

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	26.20	39.03

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LOGINID:SSSPTA1642BJF

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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
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NEWS	5	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS	6	MAY 11	KOREAPAT updates resume
NEWS	7	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS	8	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS	9	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS	10	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS	11	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and